Tissue (muscle) oxygen saturation (StO_2): A new measure of symptomatic lower-extremity arterial disease

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Objectives: **Near-infrared spectroscopy provides a noninvasive method of measuring tissue oxygen saturation and has been used to monitor extremity compartment syndrome. Tissue O_2 saturation (StO_2) is potentially useful in assessing patients with peripheral arterial disease (PAD). The purposes of this feasibility study are to (1) explore the diagnostic sensitivity of StO_2 in subjects with PAD and symptoms of intermittent claudication (IC) compared with normal subjects, and (2) correlate the change in StO_2 during and after exercise with the ankle brachial index (ABI) in patients with IC.**

Material and methods: **Forty-nine subjects, 35 normal and 14 PAD, from two centers were evaluated in a prospective cross-sectional analysis comparing StO_2 by using the InSpectra tissue spectrometer and ABI at rest (baseline) and after treadmill exercise. Measurements were obtained at baseline and peak exercise (normal subjects) and at baseline, initial claudication distance (ICD) and absolute claudication distance (ACD) in PAD subjects. Endpoint values were the mean of 15 data points. Times to 50% of StO_2 recovery to baseline (T_{50}) and complete recovery to baseline (T_{100}) were measured. Receiver-operator characteristic curves were constructed to assess the sensitivity/specificity values associated with various StO_2 cut-points.**

Results: **The PAD patients were older ($P = .0002$) and 57% were male, compared with 37% males in the normal group. The ABI was 0.68 ± 0.14 in PAD patients versus 1.14 ± 0.08 in normal subjects ($P < .0001$). The baseline StO_2 was 65% in both groups. The peak exercise StO_2 was significantly lower and the absolute change in StO_2 and the percent change in StO_2 were significantly greater in PAD patients ($P < 0.45$). The T_{50} and T_{100} were longer in the PAD patients compared to normal subjects ($P = .0001$ and .002, respectively). A T_{50} of >70 seconds yielded a sensitivity of 89% and a specificity of 85% for PAD.**

Conclusions: **StO_2 is a new and potentially useful technique to evaluate patients with PAD. Resting StO_2 was similar in PAD-IC subjects and normals. There was a significantly greater drop in StO_2 and longer recovery times in PAD-IC subjects. Interestingly, StO_2 at the ICD and ACD was similar. StO_2 offers a different and perhaps more appropriate end point for diagnosis and monitoring of the management of patients with PAD, and may offer additional insight into the pathophysiology of exercise-induced muscle ischemia and its recovery. (J Vasc Surg 2003;38:724-9.)**

Lower-extremity peripheral arterial disease (PAD) affects approximately 8 to 10 million individuals in the United States.[1] Intermittent claudication (IC) is the most common symptom of lower-extremity PAD, with approximately one third to one half of the afflicted individuals having symptoms. The annual incidence of IC is approximately 15.5 new cases per 1000 individuals.[1,2]

The diagnosis of peripheral arterial disease can generally be established with a good history and physical examination, especially if an ankle brachial index (ABI) is included as part of the physical examination. Segmental limb pressures are frequently performed by vascular laboratories and complement the ABI. Although the ABI is relatively easy to perform, its sensitivity declines from approximately 80% for severe stenosis in one or more peripheral arteries to approximately 50% for mild disease.[3] Patients with medial calcinosis will have falsely elevated lower limb pressures, and approximately one third of diabetics will have falsely elevated ABIs. In the absence of calcification, the ABI is a good measure of perfusion pressure; however, it is not an indicator of skeletal muscle ischemia, and it does not correlate with walking distance.

Near-infrared spectroscopy (NIRS) technology is used daily by clinicians to monitor the oxygenation of blood in patients at risk of hypoxia. NIRS can also provide a measure of local tissue oxygenation.[4-6] Despite its potential value as a direct method of assessing tissue ischemia resulting from arterial occlusion, little attention has been given to this technique for that purpose.

Patients with PAD of their lower extremities have symptoms of intermittent claudication as a result of exercise-induced muscle ischemia. Therefore, it is intuitively

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appropriate to use muscle oxygen saturation (StO_2) as a functional endpoint in patients with PAD and, in particular, in patients with IC.

The InSpectra tissue spectrometer (Hutchinson Technology Inc, Hutchinson, Minn) noninvasively measures and displays percent tissue StO_2, which represents a quantified percent hemoglobin oxygen saturation in a regional tissue bed. As quantification permits comparison between individuals, StO_2 has potential for providing clinically useful information about patients with ischemia caused by arterial occlusive disease.

The primary objectives of this prospective, nonrandomized study were (1) to determine whether a correlation existed between StO_2 of the gastrocnemius muscle and ABI in patients with previously diagnosed PAD causing IC, and (2) to estimate the sensitivity of StO_2 in identifying PAD in an individual subject. Secondary objectives were (3) to characterize the relationship between StO_2 and claudication symptoms, and (4) to evaluate the safety of the InSpectra tissue spectrophometer when used to screen for PAD.

METHODS

The study was approved by the Institutional Review Board of Temple University Hospital (Philadelphia, Pa) and by the Western Institutional Review Board (Olympia, Wash) for the Heart and Vascular Institute (Morristown, NJ), and each patient signed an informed consent.

Two groups of subjects were recruited for this study: normals, defined as individuals having no history or evidence of PAD, and PAD subjects whose PAD causing intermittent claudication (PAD-IC) (Rutherford Grade I) was diagnosed by vascular experts on the basis of history, physical examination, and noninvasive studies. Of the 49 subjects enrolled, 14 had PAD-IC and 35 were considered normal.

Subjects were evaluated at rest and then performed a modified Gardner treadmill protocol, walking eight 2-minute stages for a maximum of 16 minutes. The treadmill speed was maintained at 2.0 mph for all stages. The first stage was at 0% grade, and every 2 minutes, the grade was increased 2% until a maximum grade of 14% was reached. IC subjects were instructed to report their onset of symptoms (IC distance [ICD]) and the point at which they could no longer ambulate (absolute claudication distance [ACD]). Ankle brachial indices were collected prior to treadmill walking and every 5 minutes after exercise. The leg with the lowest ABI was selected as the test leg in subjects with bilateral disease. The pre-exercise ABI was considered the diagnostic ABI and used for comparison to baseline StO_2.

StO_2 was monitored with the InSpectra Tissue Spectrometer-Model 325 by means of a 35-mm light emitting/collection head attached to an optical cable placed over the selected site of the gastrocnemius muscle on the test leg. The muscle was "mapped" with the device to locate the site with the highest observed StO_2 reading . The device was adhered by means of a double-adhesive light-excluding collar and allowed to equilibrate for 5 minutes to obtain baseline reading prior to the exercise walk. Values were recorded every 3.5 seconds throughout baseline, ICD and ACD, or conclusion of a maximum 16-minute walk (normals), and for a minimum of 20 minutes for StO_2 recovery time. Baseline, ICD, ACD, and peak exercise values were represented by a mean of 15 measurements. Absolute and percent changes between baseline and peak exercise were calculated by using the baseline and peak exercise endpoints. T_{50} and T_{100} were estimated from a logistic growth curve equation estimated from the recovery StO_2 data. From the raw StO_2 data, the following endpoints were obtained:

1. Baseline
2. Peak exercise
3. Absolute and percent change between baseline and peak exercise
4. StO_2 at ICD and ACD
5. Time elapsed from peak exercise to 50% StO_2 recovery (T_{50})
6. Time elapsed from peak exercise to 100% StO_2 recovery (T_{100}).

STATISTICAL ANALYSIS

The Wilcoxon rank sum test (continuous variables) and the Fisher exact test (categorical variables) were used to test for distributional differences in demographic parameters between the study groups. To demonstrate a correlation between StO_2 and ABI, a Pearson's correlation coefficient was estimated and a linear regression model was fit to the data in order to incorporate possible confounders into the analysis and assess their effect on the relationship between ABI and various StO_2 endpoints. The effect of age and BMI were considered as possible confounders because they differed significantly among the study groups. Gender was also considered a confounder on the basis of historical differences. Analysis of variance models (one without the inclusion of the covariates and one with the inclusion of the covariates) were fit to the data to test for significant differences in the StO_2 endpoints between the study groups. This was the first step in identifying the StO_2 endpoints and associated cut-points that would differentiate the groups into PAD-IC and normal to obtain initial estimates of sensitivity and specificity. The ICD and ACD values were paired within subject, and the mean difference was compared to zero by using the Wilcoxon signed rank test. In addition, *P* values for the correlation and comparison of study group objectives were compared to an α value of .0071 ($.05/7_1$, Bonferroni method)[7] to correct for multiplicity.

RESULTS

The demographic information on the subjects is listed in Table I. Age at enrollment, body mass index, and lower-extremity ischemia category differed significantly between the PAD-IC subjects and the normal group. PAD-IC subjects (67 $\pm$ 15 years) were significantly older and had a higher body mass index (27.6 $\pm$ 3.4) than the normal

Table I. Demographics overall and for PAD-IC and normal subjects, (mean ± SD)

Parameter	*PAD-IC (n = 14)*	*Normal (n = 35)*	P *value**
Age (y)	67 ± 15	43 ± 15	.0002
Years since PAD diagnosis	3.1 ± 2.8	NA	NA
Height (in.)	66 ± 4	66 ± 5	.7239
Weight (lbs.)	170 ± 23	159 ± 37	.1102
BMI	27.6 ± 3.4	24.9 ± 2.7	.0104
Ethnic origin			
Asian/Pacific Islander	0 (0%)	0 (0%)	
Black	4 (29%)	6 (17%)	
Caucasian	10 (71%)	26 (74%)	
Hispanic	0 (0%)	1 (3%)	
Other	0 (0%)	2 (6%)	.6394
Gender			
Male	8 (57%)	13 (37%)	
Female	6 (43%)	22 (63%)	.2219
Tobacco use			
No	12 (86%)	31 (89%)	
Yes	2 (14%)	4 (11%)	1.0000
Average # of years for tobacco users	52 ± 2	10 ± 7	NE†
Rutherford lower extremity ischemia category			
Grade 0, Category 0, asymptomatic	0 (0%)	34 (97%)	
Grade I, Category 1, mild claudication	6 (43%)	0 (0%)	
Grade I, Category 2, moderate claudication	4 (29%)	0 (0%)	
Grade I, Category 3, severe claudication	3 (21%)	0 (0%)	
Missing	1 (7%)	1 (3%)	NE†

PAD, Peripheral arterial disease; *IC*, intermittent claudication.
*Wilcoxon rank sum test (*t* approximation) used for continuous variables. Fisher exact test used for categorical variables.
†Comparison between groups not evaluated.

Table II. Mean (±SD) and 95% CI of StO_2 endpoints for PAD-IC and normal subjects

	PAD-IC (n = 14)		*Normal (n = 35)*		
Parameter	*Mean ± SD*	*95% CI**	*Mean ± SD*	*95% CI*	P *Value*†
Baseline ABI	0.68 ± 0.14	0.60–.76	1.14 ±0.08	1.11–1.17	<.0001
Postexercise ABI	0.40 ± 0.21	0.27–.52	1.13 ± 0.13 (n = 34)	1.09–1.18	<.0001
Baseline StO_2 (%)	65 ± 28	49–81	65 ± 19	58–71	.9812
Duration of Exercise (min)	9.0 ± 4.8 (n = 12)		16.0 ± 0.5 (n = 34)		<.0001
Peak Exercise StO_2 (%)	9 ± 10 (n = 10)	2–16	33 ± 25 (n = 34)	24–41	.0047
Absolute Change between Baseline and Peak Exercise StO_2 (StO_2 units)	50 ± 30 (n = 10)	29–72	31 ± 21 (n = 34)	24–39	.0299
Percent Change between Baseline and Peak Exercise StO_2 (%)	76 ± 31 (n = 10)	54–98	52 ± 32 (n = 34)	41–64	.0454
T_{50} (seconds)	104 ± 39 (n = 9)	74–134	55 ± 23 (n = 33)	47–63	<.0001
T_{100} (seconds)	203 ± 69 (n = 8)	146–261	117 ± 63 (n = 27)	92–142	.0020
Recovery as a Percent of Baseline	117 ± 64 (n = 12)	77–158	119 ± 37 (n = 34)	106–132	.8951

PAD, Peripheral arterial disease; *IC*, intermittent claudication; *StO_2*, muscle oxygen saturation; *ABI*, ankle brachial index.
*95% Confidence interval (*CI*) based on normal approximation.
†F test for variable indicating PAD-IC and normal status (not corrected for cavariates).

subjects (age 43 ± 15 years, BMI 24.9 ± 27). As expected, PAD-IC subjects had lower-extremity ischemia categories consistent with intermittent claudication, and normal subjects did not. Height, weight, gender, and race were not found to be different between the groups.

The results for the parameters measured are presented in Table II, which reports the mean (±SD) and 95% confidence intervals of StO_2 endpoints for PAD-IC subjects and normal subjects. As expected, there was a significant difference in the resting ankle brachial index; however, there was no difference in StO_2 measurements at rest. The StO_2 values versus ABI plotted over time are depicted in Fig 1 for the normal group and Fig 2 for PAD patients. Peak exercise StO_2 was significantly lower in the PAD-IC

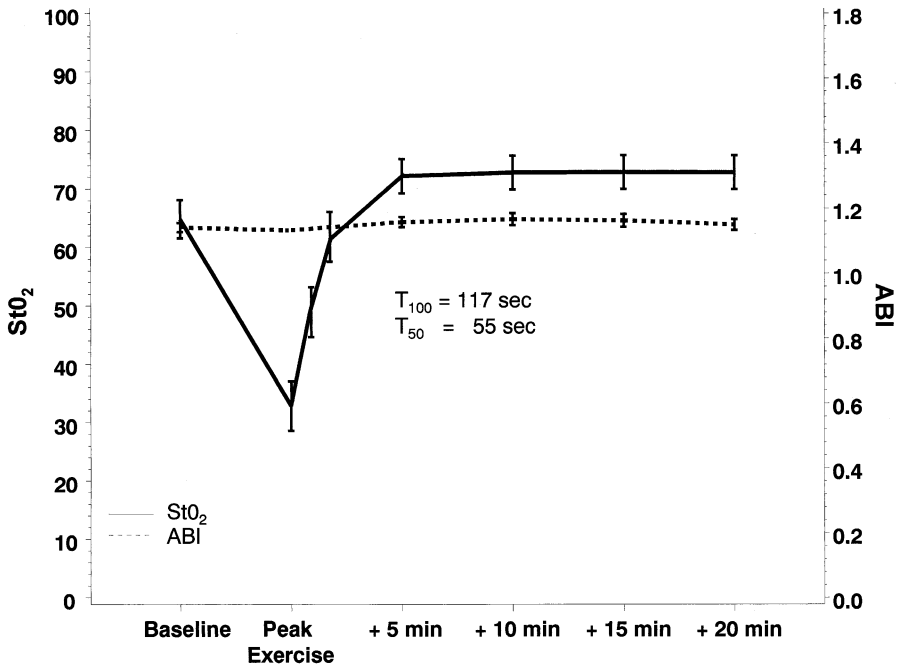

Fig 1. Mean ± SEM for muscle oxygen saturation (*StO$_2$*) and ankle brachial index (*ABI*) throughout exercise protocol for normal subjects (n = 35).

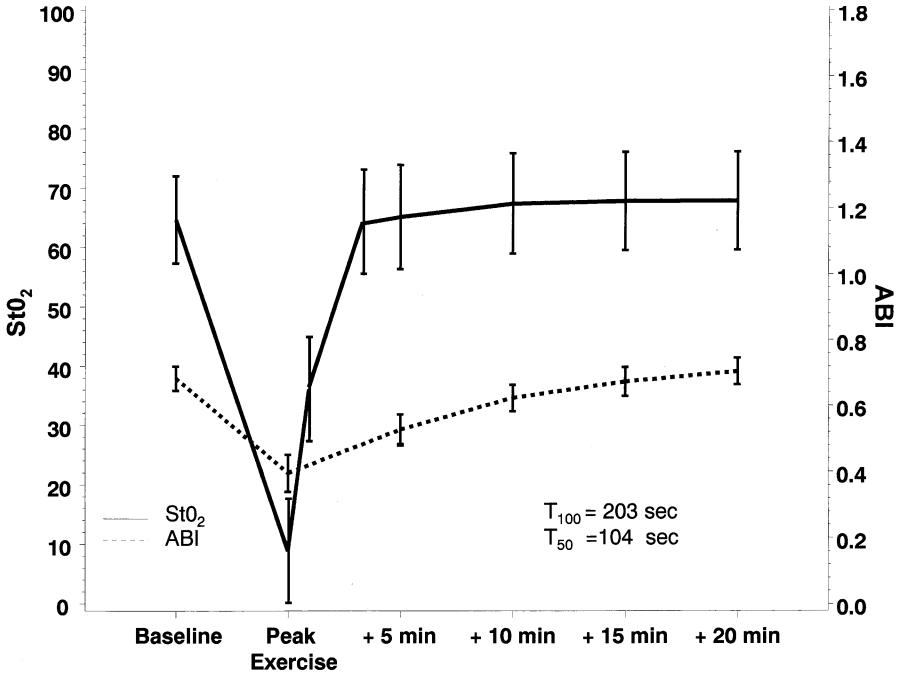

Fig 2. Mean ± SEM for muscle oxygen saturation (*StO$_2$*) and ankle brachial index (*ABI*) throughout exercise protocol for PAD-IC subjects (n = 14).

group. The absolute change in StO_2 between baseline and peak exercise as well as the percent change from baseline to peak exercise was significantly greater in the PAD-IC group compared with the normal group. However, the peak exercise, absolute, and percent change in StO_2 results did not persist once the covariates of age and gender were included in the model. The StO_2 recovery time was significantly longer both at the 50% value (T_{50}) and time to return to baseline

Table IV. Initial claudication distance (*ICD*) and absolute claudication distance (*ACD*) and the associated muscle oxygen saturation (StO_2) values and walking times in PAD patients

	ICD (mean ± SD)	*95% CI*	*ACD (mean ± SD)*	*95% CI*	P *value**
StO_2	10 ± 11 (n = 8)	3-18	8 ± 11 (n = 8)	0-18	.27 (n=8)
Walking time	5.9 ± 3.9 (n=14)	3.7-8.2	7.6 ± 3.9 (n=10)	4.8-10.4	

*Wilcoxon signed rank test.

(T_{100}) in the PAD-IC group. These results did maintain statistical significance upon inclusion of covariates and upon correction for multiplicity by using the Bonferroni method.

A significant correlation was found between ABI and T_{50} ($r = -.65$, P value $< .0001$) and T_{100} ($r = -.48$, P value $= .0035$). These results maintained statistical significance upon inclusion of covariates and upon correction for multiplicity by using the Bonferroni method (Table III, online only).

Receiver-operator characteristic curves (ROC) were used to assess the sensitivity and specificity values associated with various StO_2 cut-points. Sensitivity was defined as the proportion of subjects testing positive for PAD-IC status when an StO_2 endpoint was used for the subjects known to have PAD-IC in the study. Specificity was defined as the proportion of subjects testing negative for PAD-IC status when an StO_2 endpoint was used for the subjects known to be normal in the study. The StO_2 endpoints used to differentiate the groups were T_{50} and T_{100} based on the strength of the ROC results. The T_{50} cut-point maximizing sensitivity without losing specificity was $T_{50} \geq 70$ seconds, which yielded a sensitivity of 89% (8/9) and a specificity of 85% (28/33). When T_{100} was evaluated, a value of ≥165 seconds gave the best sensitivity/specificity estimate of 88% (7/8) and 81% (22/27), respectively.

The ICD and ACD in PAD patients are listed in Table IV. There is no significant difference between the two values.

There were no adverse events when the InSpectra tissue spectrometer was used, further supporting the safe use of this noninvasive, painless device.

DISCUSSION

NIRS is based on the ability of tissue to absorb infrared light. Light in the near-infrared spectrum passes easily through skin and bone; however, it is variously absorbed by tissues containing blood. This is predominantly determined by chromophores in tissue whose capacity to absorb infrared light is dependent on oxygen content. Changes in the amount of near-infrared light reflected by tissue can be analyzed to detect the percentage oxygen saturation of hemoglobin in tissue (muscle). It is reasonable to apply this technology to the evaluation of patients afflicted with any condition or disease causing tissue ischemia.

The primary objectives of this study were to evaluate the correlation of StO_2 with ABI and to estimate the diagnostic sensitivity of StO_2 in differentiating subjects with and without peripheral arterial disease. We thought that a 16-minute Gardner protocol would reveal the muscle ischemia in PAD patients while being a vigorous but not necessarily fatiguing exercise for subjects in the normal group.

The resting StO_2 did not correlate with resting ABI in PAD-IC patients compared to the normal group. This is not surprising, and actually, it was anticipated, because it is known that leg blood flow at rest is not different in PAD-IC patients compared with normal subjects. However, there was a significant difference in the peak exercise StO_2, both in terms of an absolute drop and a relative change in StO_2, and a significant difference in their recovery times, both at T_{50} and T_{100}, when PAD-IC patients are compared with normal subjects. The exercise results did not persist once the model was expanded to include covariates (age, BMI, gender). Therefore, it is not statistically possible to know whether the difference found was due to PAD status or age, although in the authors' opinion, PAD status was the significant factor. As the T_{50} and T_{100} results persisted after incorporation of the covariates, this assumption appears well founded. The accuracy of StO_2 in detecting PAD-IC versus normal was good, yielding an 89% sensitivity and 85% specificity with a T_{50} of ≥70 seconds. Because of the relatively small number of enrolled subjects, validation of these initial estimates is not possible.

Using venous occlusion plethysmography to calculate muscle blood flow, other investigators included NIRS to evaluate oxygen consumption, oxygen resaturation, and recovery times.[7] These investigators also observed a high correlation of oxyhemoglobin recovery time with the ABI after walking exercise, concluding that NIRS appeared to be an effective, noninvasive method of evaluating oxygen demand and delivery in leg muscles of PAD patients at rest and during exercise. The NIRS technology used by Kooijman et al[8] was different than that used in this study, in that those investigators measured relative changes in the oxygenation of the chromophores involved with oxygen binding rather than a quantitative oxygen saturation of muscle tissue. We believe that the quantitative method used in this study offers the advantage of comparison among patients, patient groups, and disease states.

The design of this study incorporated maximal exercise for PAD-IC patients and vigorous exercise in normal subjects (through eight stages of a Gardner protocol). Evaluating the response of both groups raises the question as to whether a much less vigorous exercise would be more appropriate and raises the question as to whether the slope of the fall in oxygen saturation during graded submaximal

exercise might be a better indicator of ischemia caused by arterial occlusive disease, especially in patients with IC.

Figure 2 graphically shows the significant drop in StO_2 with exercise in PAD patients, a drop that is many magnitudes greater than the corresponding drop in ABI, which suggests improved sensitivity in detecting exercise-induced muscle ischemia and improving the evaluation of patients with intermittent claudication.

There was overlap in the exercise StO_2 endpoints in some normal subjects with PAD-IC patients. Some normal subjects had their StO_2 fall to unexpectedly low levels. It is possible that some of these normal subjects had subclinical arterial occlusive disease not previously detected and that any fatigue or aching response to exercise was attributed as a normal response to vigorous ambulation rather than as a suspicion of underlying pathology.

StO_2 has been investigated in the diagnosis and management of patients with compartment syndrome of the leg, because muscle ischemia is the basis for intervention. Similar to patients with PAD, patients with compartment syndrome may have reduced systemic oxygen delivery, which might affect StO_2 readings. Arbabi et al[9] demonstrated in an animal model that StO_2 clearly differentiated the muscle ischemia caused by systemic hypoxemia and shock from that caused by the more advanced ischemia of compartment syndrome. Giannotti et al[10] reported on the use of NIRS-derived StO_2 values in the lower extremities of trauma patients with compartment syndromes. They demonstrated that StO_2 was diminished in patients with compartment syndrome and normalized after fasciotomy. Van den Brand et al[11] report significant differences in average peak exercise values and percent change from baseline between patients with chronic exertional compartment syndrome (CECS) and normal subjects. Interestingly, the StO_2 values of patients with CECS returned to the normal range postfasciotomy. As muscle ischemia is the important component in both compartment syndrome patients and PAD-IC patients, StO_2 measurements would appear to have substantial utility in both groups.

The observations made in this feasibility study of normal subjects and PAD-IC subjects raise more questions than are answered regarding the utility of this technique. Modifying the investigative method, evaluating the effect of systemic hypoxemia on exercise response, studying patients during submaximal exercise, and studying the proper application of StO_2 in patients with critical limb ischemia before and after revascularization are but a few of the potential areas of investigation. As StO_2 is a direct assessment of tissue oxygen saturation, it has significant potential to offer insight into the pathophysiology of a wide variety of conditions causing peripheral ischemia, especially exercise-induced muscle ischemia and its recovery.

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